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CHAPTER 10

Some Computer Techniques of Value for Study of Circulation

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I. INTRODUCTION

Analog and digital computers are becoming powerful tools for study of self-regulation in the circulatory system. Although the study of circulation has probably received more attention from physiologists than any other physiologic system, it has resisted quantitative description in spite of these efforts largely due to lack of the necessary tools for analysis and, until recently, a lack of the necessary transducers and techniques of measurement. The difficulties in analysis arise from the fact that the circulation is a closed-loop, nonlinear control system with many elements involved. For these reasons it does not lend itself readily to purely intuitive analysis. It is the purpose of this chapter to point out through examples some

techniques involving analog and digital computers which have been used in recent years to investigate the physiologic control mechanisms which affect the circulation.

The computer system used in the examples presented in this chapter is composed of a centrally located analog computer, analog-to-digital convertor, digital computer, digital-to-analog convertor, analog tape recorder, and a system of "remote stations."

The analog computer (Philbrick Researches, Inc.) consists of functional units, each of which contains two operational amplifiers with built-in feedback resistors and capacitors which permit up to four inputs to be added and/or integrated. The initial conditions and the sign and gain for each input may be controlled by built-in decade switches. Start of solutions may be controlled by a central unit which also generates the sweep of a large-screen oscilloscope display through a 30-volt clamp. This clamp can be used to control external devices such as the analog-to-digital convertor. The analog computer control device in turn can be triggered from the digital computer by way of the digital-to-analog convertor. Since the analog computer is composed of largely self-contained operational units and is not tied to a central problem board, expansion is completely flexible and can be accomplished as the need arises. Banks of ten operational amplifiers in a single 10-inch rack panel may be equipped with front panel plug-ins to perform semipermanent functions in the laboratory, such as the track and hold circuits described in this chapter.

The general purpose digital computer (Control Data 3200) has 32,768 24-bit words and a basic cycle time of 1.25 microseconds. The upper 4000 words contain a monitor program which permits the multiplexing of the central processor and input/output among the several programs located in memory at any one time. The lower 16,000 words are used for FORTRAN and assembly language compilations which are read from a card reader following a manual interrupt by the operator and are listed on the printer. This compilation can proceed while real-time programs are being executed in the upper half of memory. After compilation a program may be run directly and/or stored on the program tape. If an older version of this program is already on the tape, the new version replaces it.

Programs designed to run in real time with data generated in one of the laboratories may be called from the program tape into memory from the appropriate laboratory. The investigator in that laboratory dials on a four-digit octal switch a code number representing his program. He then presses an interrupt button which loads this program from the program tape into a 4000-word area of memory reserved for that laboratory. Control is transferred to the beginning of his program and the program is executed to the point where a message is displayed in the form of alphanumeric characters

on the face of an oscilloscope with a long persistent "memory" tube (Tektronix Model 564). He may then specify program options or model parameters through this digital switch and send data to the computer through the A-to-D convertor at the appropriate times during his experiment. The multiplexer for the A-to-D convertor is controlled through the digital computer program. Likewise the sampling rate is specified in the digital program and the internal clock (10 kc) interrupts this or any other program at the appropriate times to sample the analog data. Up to three programs may use the analog-to-digital convertor simultaneously, each one sampling different analog channels at different rates from the other. Two banks of twenty-four relays and digital switches can be operated under computer control to control the flow of information (graphs and digital print outs) to the appropriate oscilloscopes or to the analog computer.

II. ON-LINE DATA REDUCTION

In the studies reported here transducers are utilized which convert a physiologic variable in the experimental animal or human to a voltage which is varying as a function of time. Data reduction is defined as the process which converts this voltage into a form which is more meaningful to the investigator than the original data. Any form of data reduction involves characterization of the data in terms of a model preconceived by the investigator. Information is always lost in the process since real data never can be completely described by a model. For this reason, it is often desirable to preserve the original raw data in a form which permits subsequent analysis using a different model. The decision as to whether to make the additional effort and to accept the expense involved in recording the direct output of the transducers on magnetic tape during an experiment, as a backup to the on-line data reduction being performed, will depend largely upon the ease with which the experiment itself can be reproduced.

A. Averaging over One Heart Cycle

An electromagnetic flowmeter was placed around the ascending aorta of a dog. Through a carefully machined hole in the flowmeter a #20 needle was introduced through one wall of the aorta so that its tip lay in midstream with the bevel facing laterally. The hub of the needle was connected to a small polyethylene tube which was brought out through the chest between the scapulae along with the lead wires from the flowmeter. This tube could be connected to a strain gauge which the dog carried on his back during the experiment. The tube, needle, and gauge were filled with heparinized saline. In Fig. 10-1 is shown the output of the pressure and flow

transducer as a function of time recorded from a dog standing at rest. It was the object of this experiment to study the effects of exercise on stroke volume, heart rate, cardiac output, mean arterial pressure, and resistance. A diagram of the analog computer arrangement used to reduce the original

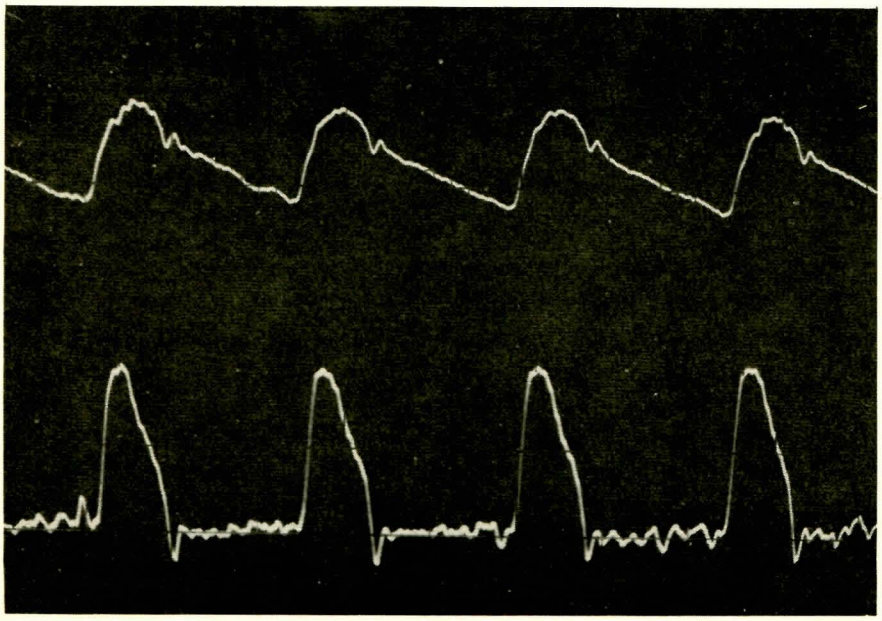


FIG. 10-1. Aortic pressure (upper trace) and flow (lower trace) in a standing dog at rest.

flow and pressure signal to a graph of these derived variables as a function of time is shown in Fig. 10-2.

This shows the logic used to trigger a series of track and hold circuits, shown at the bottom, at the end of each systole (Warner, 1962). The aortic flow curve is differentiated and rectified so that only the rate of decrease in flow appears at the point labeled ② on the diagram. A constant bias voltage is subtracted from this rectified derivative and the difference is integrated. At the point where the integral exceeds zero a switch consisting of an operational amplifier with only a diode in the feedback loop suddenly jumps from zero voltage to saturation. This trigger voltage at point ④ closes a relay which is normally open to reset the integrator and the same pulse triggers a sawtooth generator. This sawtooth generator controls the firing of two pulse generators, ⑥ and ⑦. The pulse at point ⑧ occurs first; this is subtracted from a constant voltage and fed to a relay which allows

the whole circuit to track for 1 millisecond the output of the first amplifier of the two labeled track and hold circuit. This relay then opens, and, since there is no discharge path for this feedback capacitor, the final voltage on the integrator will be held until the relay is closed at the end of the next

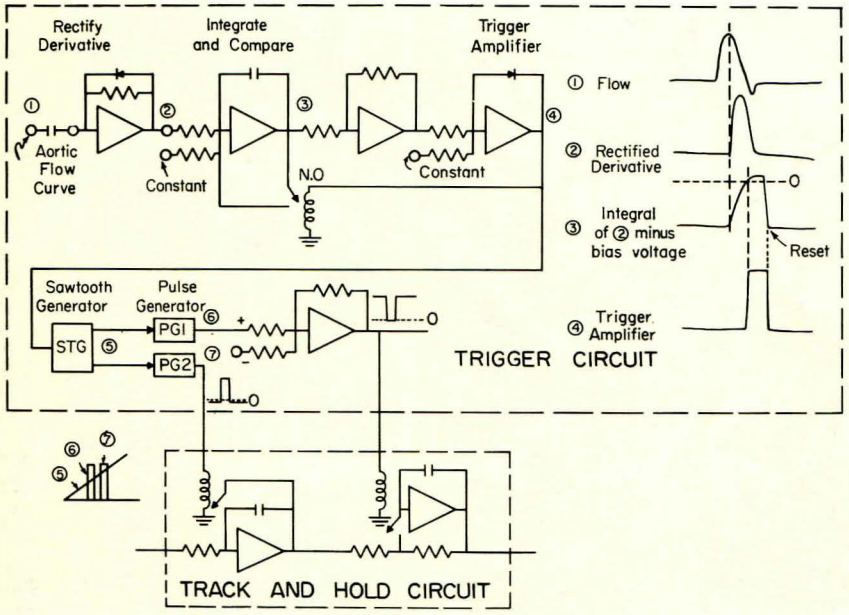


FIG. 10-2. Analog computer setup for calculation of circulatory parameters from data shown in Fig. 10-1.

heart cycle. The second pulse at point ⑦ then occurs and this resets the integrator to its initial condition. In the techniques used here three such track and hold circuits are controlled by a single trigger circuit. A constant is integrated by one to obtain a voltage proportional to the duration of the heart cycle. A second one integrates flow to obtain the stroke volume and a third integrates the pressure to obtain mean pressure over each heart cycle. Cardiac output and peripheral resistance can be derived from these variables using multiplier and divider elements as shown in Fig. 10-15.

The choice of one heart cycle as the time over which to average in this case is obvious since this is the minimum interval over which these variables can be defined. This averaging process destroys information about the time course of flow and pressure. Another kind of averaging can be used to advantage to bring out the details of the contour of a pressure or flow wave in the presence of random noise. An example of such a situation is illus-

trated in Fig. 10-3 which shows a recording of the pressure and flow signals obtained from a dog running on a treadmill. The artifact superimposed on the arterial pressure tracing is due to the movement of the catheter system which transmits the pressure wave from the aorta to the strain

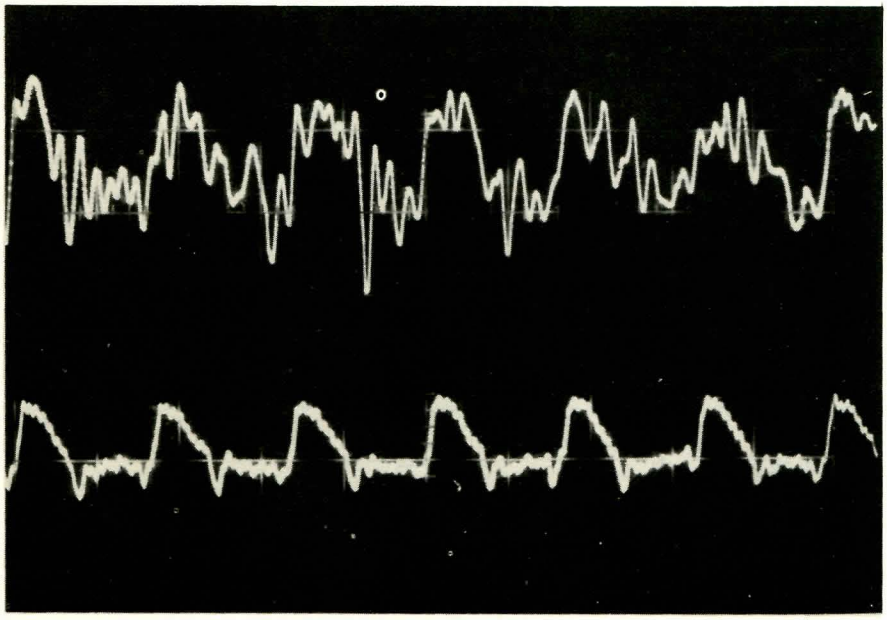


FIG. 10-3. Aortic pressure and flow signals from a running dog. Note large movement artifacts, particularly in the pressure signal (upper trace).

gauge. In Fig. 10-4 is shown a plot of the average pressure and average flow as a function of time for each point in the heart cycle. This was obtained by sampling the direct output from the pressure and the flow transducers at 100 cycles per second through an analog-to-digital convertor directly into a general purpose digital computer. The digital computer is programmed to continually accept pressure and flow data by interrupting its calculations on this or any other program that might be running every 100th of a second to sample both data channels.

The program to accomplish the averaging first finds the point on the rising limb of each flow curve where flow reaches one-half its peak value during that cycle. Five is then subtracted from the index to define the beginning value. Each successive point on the pressure and flow curves is added to the corresponding points on the average pressure and average

flow arrays which were originally set to zero. This is repeated for sixteen heart cycles. Then each value in the average array is divided by 16 and the averaged pressure and flow arrays are fed out through a digital-to-analog convertor and displayed on an oscilloscope. The oscilloscope has a

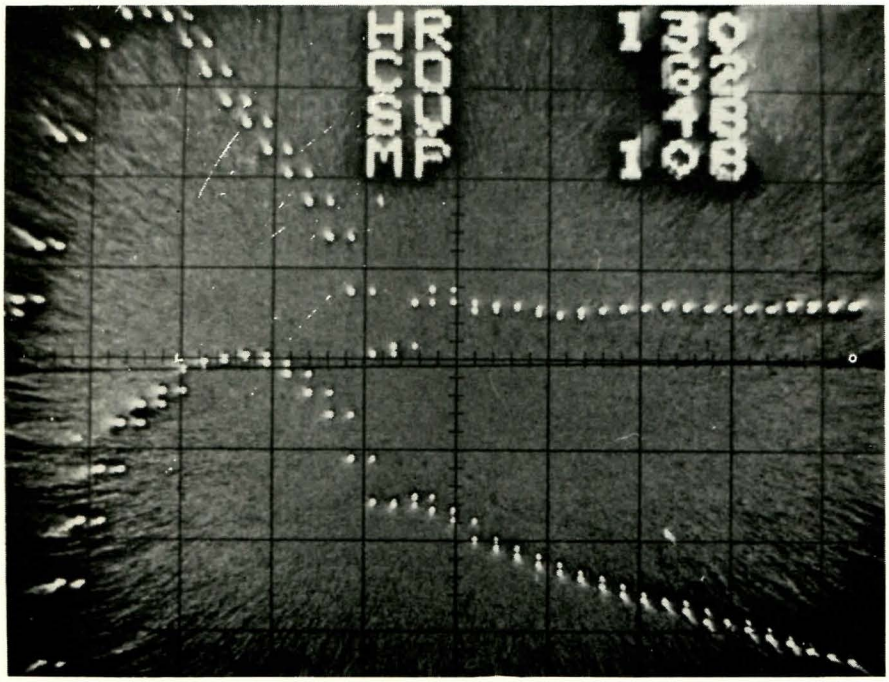


FIG. 10-4. Averaged pressure (lower trace) and flow (upper trace) data, showing improvement due to averaging process.

"memory tube" which provides for long persistence of this trace. These average wave forms may also be used for further computation in the computer as will be described later in this chapter. Notice that the part of the original signal which is not systemically related in time to the heart cycle largely disappears from the averaged wave forms.

Another example of averaging is illustrated in Fig. 10-5. In this experiment a single nerve fiber of the carotid sinus nerve was dissected out under a microscope and placed across two platinum wires for detection of electrical activity in the nerve as a function of time. Since the nerve was severed and the recording electrodes placed across the segment connected to the carotid sinus, the frequency of action potentials on this fiber was a measure of the output of the carotid sinus. The input to the carotid sinus stretch

receptor is the pressure in the carotid artery. The raw data from this experiment then was the pressure in the carotid sinus and the action potentials recorded from the carotid sinus nerve.

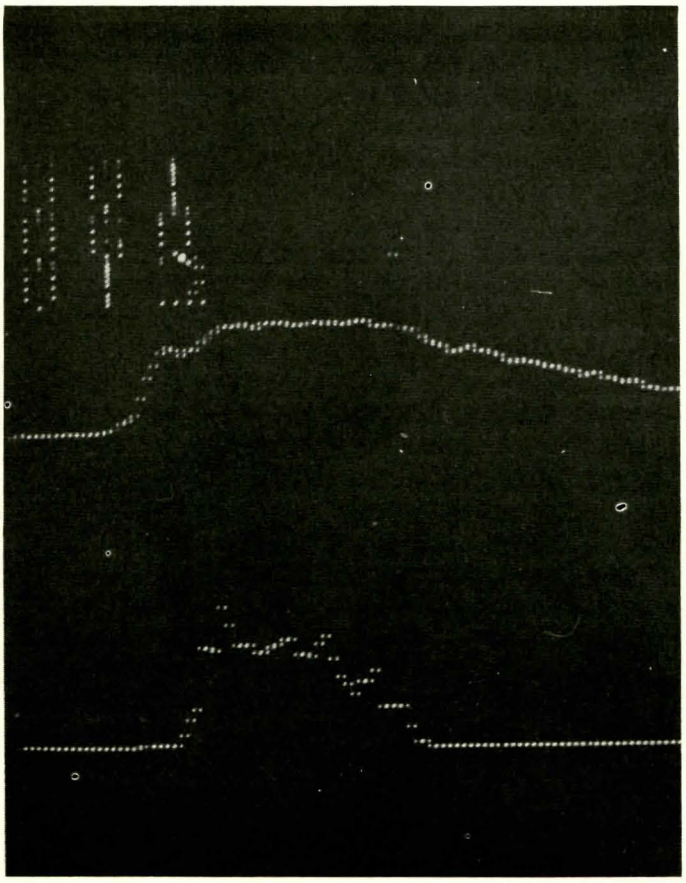


FIG. 10-5. Computer averaged data on frequency of discharge of carotid sinus nerve (lower trace) compared with arterial pressure (upper trace).

The pressure was sampled by the computer at 100 samples per second through the analog-to-digital convertor. The voltages recorded from the nerve fiber were amplified and fed to an analog computer. Each time the voltage on the nerve exceeded a preset threshold, the analog computer generated a pulse which interrupted the digital computer and caused the internal clock in the computer (which runs at 10,000 counts per second) to be sampled. The clock reading at the time of the preceding action

potential was then subtracted from this value and the difference stored in memory as the time between action potentials. The reciprocal of this time is taken as the instantaneous firing rate of the nerve fiber.

Pressure is averaged with succeeding heart cycles to obtain the average pressure at each point during the heart cycle using similar logic to that described above to identify the onset of each systole. The average frequency of firing of the nerve at each point in the heart cycle is generated and displayed along with the "averaged" pressure wave form on an oscilloscope. In this case, however, the oscilloscope is not used in the long persistent mode and the average wave forms are displayed at 0.01-second intervals on the oscilloscope so that the investigator can see these wave forms develop in time. Once these average wave forms have stabilized the investigator can, by pressing a manual interrupt, cause them to be recorded on digital tape for later analysis.

B. Interval and Amplitude Distributions

In an experiment such as the one just described, it is necessary for the investigator to know when his recorded action potentials are arising from a single nerve fiber. This cannot be done from anatomical criteria. It is generally agreed by neurophysiologists that the amplitude of successive action potentials arising from a single nerve fiber is constant. Of course, as with any other biological signal, there is noise superimposed on the recording which, if random, would be expected to cause the distribution of amplitudes of a series of action potentials to be normally distributed around some average value. Figure 10-6 shows such a distribution of amplitudes for 1000 action potentials recorded over a period of a few seconds from a carotid sinus nerve fiber. Once again the computation is performed using a hybrid analog and digital system. The electrical signal from the nerve is amplified and fed to the analog computer where it is compared to a preset reference level. Each time the signal exceeds this reference a 1-microsecond pulse is generated which interrupts the digital computer. The digital computer then samples for 2-milliseconds at 50,000 samples per second through the A–to–D convertor. This series of samples is scanned in the digital computer to find the maximum value. The clock reading corresponding to the maximum is stored. The previous clock reading is subtracted and this difference stored in an array of intervals. Likewise, the maximum amplitude is stored in an amplitude array. After 1000 action potentials have been so analyzed the distribution of amplitudes is displayed on the "memory" oscilloscope. If this distribution is multimodal, it indicates that more than one nerve fiber is contributing action potentials to the recording and the investigator continues with the dissection in search of a single fiber.

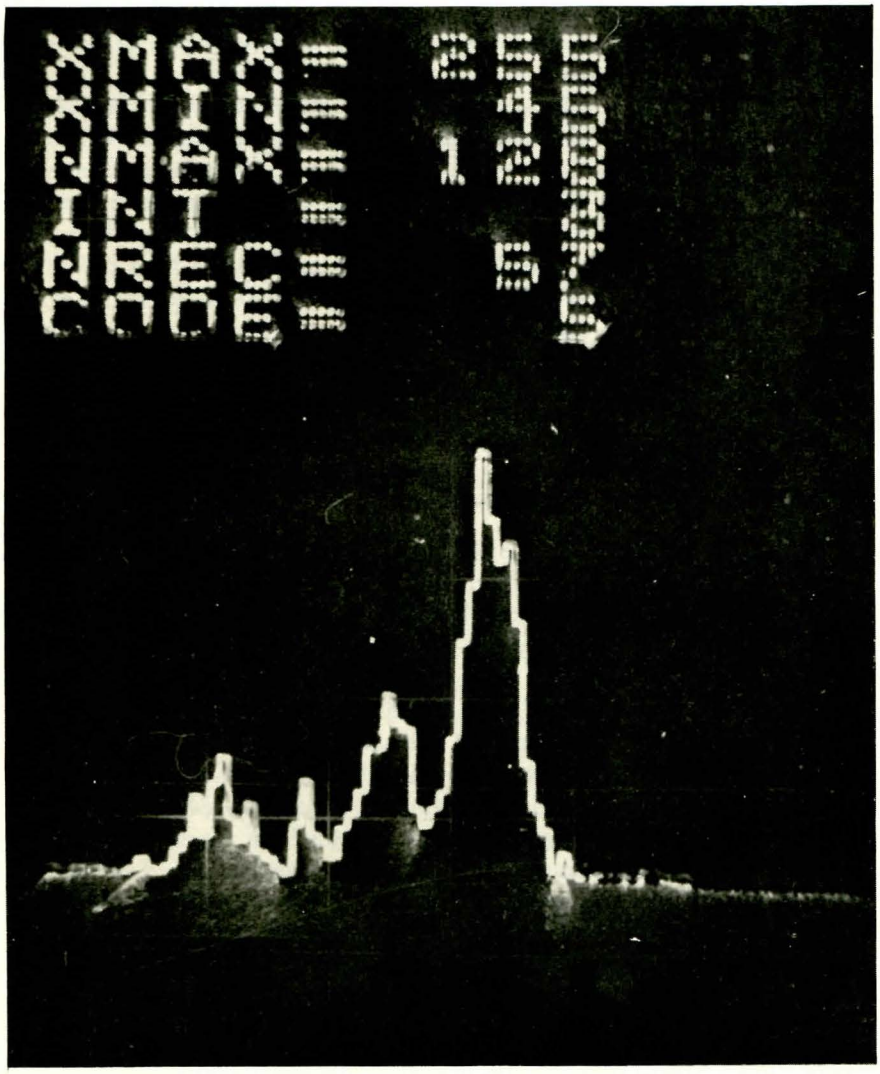


FIG. 10-6. Amplitude histogram of discharges in carotid sinus nerve.

C. Cardiac Output Estimation

Another form of data reduction of particular value in studying the circulation in humans is the measurement of cardiac output by indirect means. Two examples of this will be described.

Cardiac output can be calculated from the time course of indicator concentration in blood recorded downstream in the circulation following a sudden single injection of a known amount of indicator upstream (Zierler, 1962). To do this, however, requires extrapolation of the descending limb of the indicator dilution curve to predict the time course of indicator concentration that would have occurred at the recording site had not some of the indicator recirculated and passed the recording site a second time before all of the indicator had passed the first time. The generally accepted method for extrapolation involves finding that part of the descending limb which best fits an exponential decay. This is done by successively searching down the descending limb for a 3-second interval which not only best fits an exponential equation but also satisfies the condition that the extrapolated concentration–time curve should not exceed the recorded concentration at any point further down the curve. Integration of the curve is then performed and a calculation of cardiac output and certain other derived parameters of the circulation is carried out. Because these calculations can be done by hand and because approximately 40 seconds is required for the curve to be generated at the recording site following injection, it is difficult to justify use of a high-speed digital computer for performing this operation if the computer must be completely occupied with doing only this during the whole 40 seconds. However, a program has been developed for time sharing which permits the procedure to be carried out while other computation is proceeding in the computer. The computer is occupied only for a few microseconds each time a sample is obtained (64 times per second) during the 40 seconds required to generate the data. After the data is in the computer, less than 1 second of computer time is required to complete the whole calculation and display on a memory oscilloscope back in the laboratory the numerical results of the calculation as well as a plot of the recorded time course of indicator and, superimposed on this, the extrapolated indicator concentration curve (Fig. 10-7). This time sharing mode of computer operation is ideally suited for many kinds of laboratory procedures which take long periods of time to occur and yet involve computations which require only a small amount of computer time.

Another example of indirect estimation of cardiac output as a means of real-time data reduction in the study of the circulation is the calculation of stroke volume from the aortic pressure wave curve (Warner *et al.*, 1953).

This method has proven especially useful in carrying out studies of cardiovascular control to human subjects. The output of the pressure transducer is digitized at 100 samples per second and sent directly to the computer. A pattern recognition program identifies the onset and end of

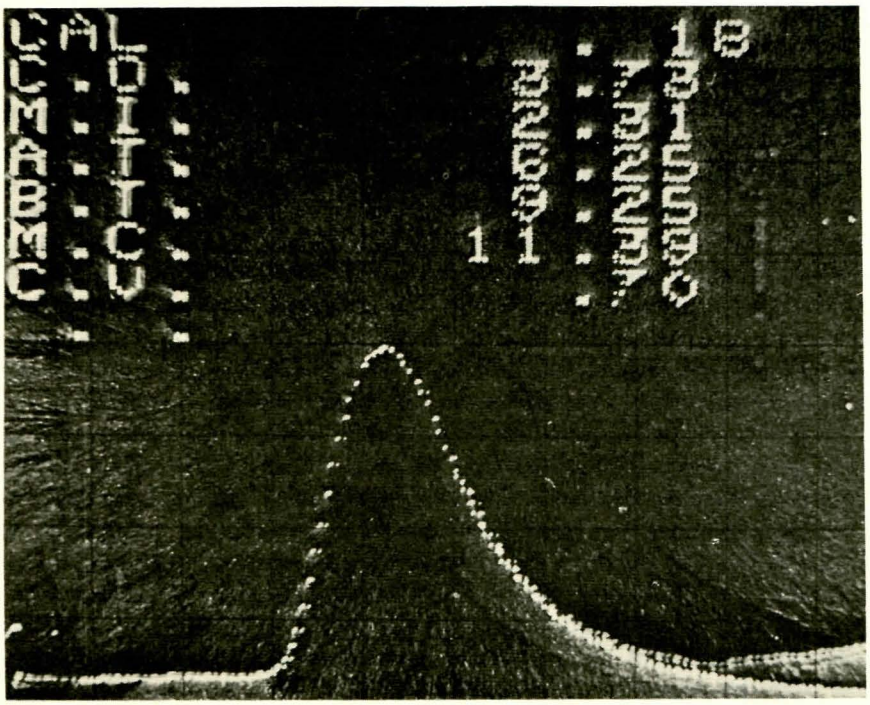


FIG. 10-7. Computer output of indicator concentration curves and calculation results in cardiac output determination.

each systole in order that the four definite integrals called for by Eq. (1) may be obtained:

$$SV = K(a_3 - a_1)\left(1 + \frac{a_1 + a_2}{a_3 + a_4}\right). \tag{1}$$

SV is the stroke volume and the terms labeled a_1, a_2, a_3, and a_4 are the definite time integrals of pressure (minus 20 mm Hg) with respect to time as shown in Fig. 10-8. t_2 and t_4 are the beginning and end of systole while t_1 and t_3 precede two times by 0.1 second. The term K in Eq. (1) is derived experimentally by calibrating against an independent measurement of cardiac output during a steady state by the indicator dilution technique. Once the method has been calibrated in such a way, each subsequent aortic pressure pulse can be used to estimate the stroke volume. Since the calculations can be performed easily in real time, continuous monitoring of stroke volume can be performed for an indefinite period. Once again the time sharing mode of computer operations makes this feasible since other

programs (i.e., a FORTRAN compilation) can proceed in the machine at the same time. A comparison of pressure pulse and dye method is shown in Fig. 10-9.

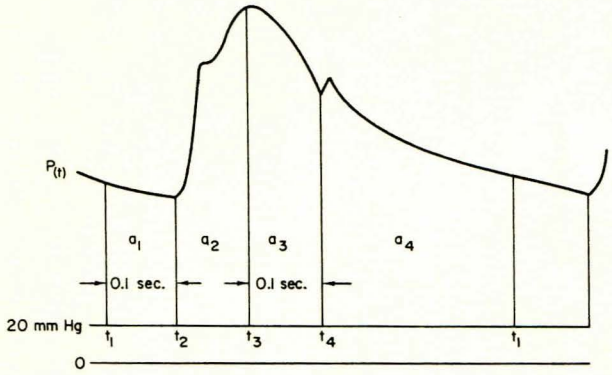


FIG. 10-8. Aortic pressure pulse contour, divided for calculation of stroke volume.

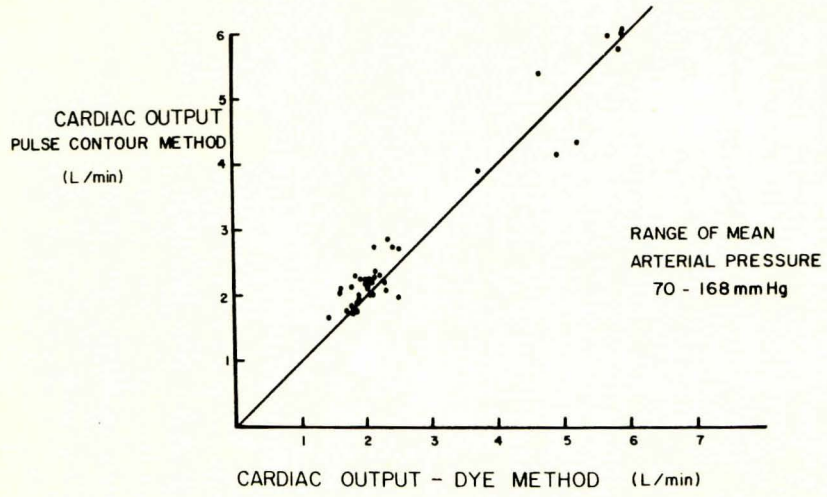


FIG. 10-9. Comparison of cardiac output values obtained by dye dilution and pulse contour methods.

III. THEORETICAL MODEL

Based on some observations made using the techniques just described, the model of cardiac output control shown in Fig. 10-10 was devised (Warner *et al.*, 1964). Each of the boxes in the diagram indicates the link

between the input and output of an element of the system and may be represented in mathematical form. A quantitative description of some of these links has already been accomplished, while others are still only known in a qualitative way. The symbol *M* indicates multiplication of two inputs to produce the output.

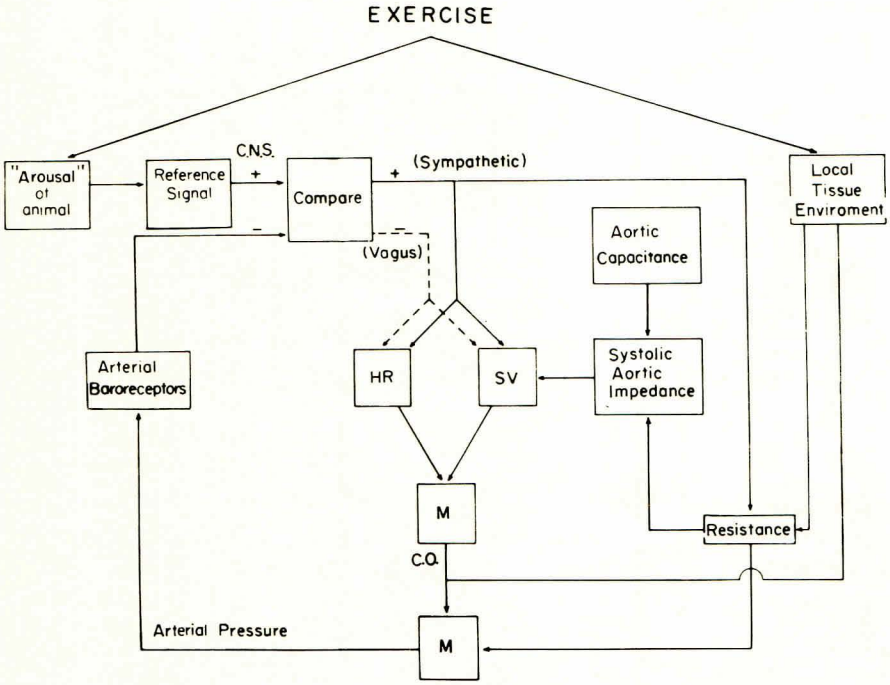


FIG. 10-10. A model of a cardiac output control system.

The theory states that exercise initiates two trends of events. First, the animal is aroused and this level of arousal determines a reference signal to be compared in the nervous system (probably in the brain stem) to the incoming action potentials of the baroreceptors. Rushmer and Smith (1959) and others have demonstrated this phenomenon in the form of an increase in heart rate occurring in the conditioned animal as the experimenter reaches for the switch to start the treadmill. This arousal phenomenon is more prominent in some dogs than in others and the extent of response is quite predictable from one day to the next.

The second major result from the onset of exercise is an increase in metabolic activity in the exercising muscles. The local chemical environment in these muscles is determined by the level of aerobic and anaerobic

metabolism and by the blood flow. As the increased rate of metabolism changes the chemical environment in the exercising muscles, vasodilitation results which is refractory to efferent sympathetic vasoconstrictor activity. Since the vascular system is a parallel network this will result in a fall in total peripheral resistance. Since, by definition of resistance, mean pressure is the product of resistance and cardiac output, a fall in resistance will result in a fall in arterial pressure unless cardiac output has already increased. This fall in pressure is sensed by the pressure receptors resulting in a decrease in traffic of action potentials on the afferent nerves from the receptors to the center in the brain stem. It is postulated that here in the central nervous system (CNS) the signal from a baroreceptor is compared to a reference signal. The sympathetic efferent outflow and the vagus outflow are related to the difference resulting from this comparison, the sympathetic directly and the vagus inversely, Because the sympathetic outflow is ineffective in bringing about a sustained reflex vasoconstriction in exercising muscles, the arterial pressure must be restored through an increase in heart rate and/or stroke volume until mean arterial pressure is high enough that the signal from the baroreceptors equals the reference signal in the CNS comparator.

A second and even more important effect of the vasodilitation and fall in the resistance that occurs with the onset of exercise is the direct influence of the decreased hydraulic impedance on stroke volume. The left ventricle as a pump will eject during systole an amount of blood which depends inversely on the opposing forces generated in the arterial bed during systole as a result of the blood entering the arterial bed (Warner, 1959). This opposing force will depend not only on the resistance to blood flow but also on the capacity of the arterial bed to store the ejected blood during systole by distension of its walls. Thus, it is a complex hydraulic impedance which involves both resistive and capacitive terms which must be considered in evaluating this process.

In the following sections of this chapter experiments will be described which were designed to test this hypothesis and to provide quantitative information regarding the input output/relationship of certain components of this system. These experiments rely heavily on computer techniques.

IV. INPUT-OUTPUT RELATIONSHIP

In order to build a mathematical model of the system described above, it is first necessary to describe the relationship between input and output as a function of time for each element in this system (Warner, 1964). If the system were linear, the input/output relationship could be expressed in the form of LaPlace transforms. This might make it possible to obtain an

analytical solution for certain types of forcing functions and a variety of useful techniques have been developed by engineers for analyzing such systems. However, this system, like most other biological systems, has many nonlinearities, and in fact it is these nonlinearities which dominate in determining the system's behavior. For this reason analytical solutions are hardly worth pursuing and simulation of the system on a computer becomes the most direct approach.

A. Model of Heart Rate Control by Sympathetic and Vagus Efferent Information (Warner and Cox, 1952)

The first step in devising a model is to observe the relationship of the output variable to time which results from a known time course for the input variable. In the present case, to describe the relationship between the output of the system (heart rate) and the input (frequency of action potentials on the sympathetic efferent nerves to the heart, f_1), the following procedure was used. First, recordings were made of the output response (HR) resulting from step increase and decrease in the input variable f_1. The heart rate response to two-step inputs in f_1 of two different magnitudes is shown in Fig. 10-11. Several features of this response can be noted which

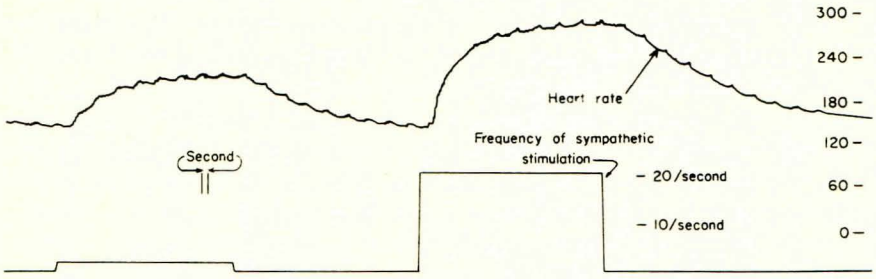
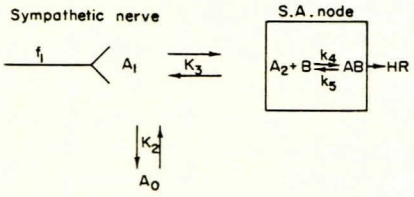


FIG. 10-11. Effect of sympathetic stimulation on heart rate, showing features required in a model.

must be accounted for by the theory. First the heart rate response is asymmetrical, rising to a plateau value faster than it falls back to the control level after stimulation is stopped. Second, the rate of increase of heart rate following a sudden increase in frequency (f_1) of stimulation is dependent upon f_1. Finally, it can be seen that the steady-state response is nonlinear. The maximum change in heart rate resulting from stimulation at 2/second is 50% of that resulting from stimulation at 20/second. The next step in formulating an hypothesis to describe such a system consists of drawing a block diagram to represent the physical and chemical processes thought to

comprise this system. In doing this, all available information concerning the system should be used in order that the final model found to describe the kinetic properties of the system may realistically account for the other properties known to be present.

In Fig. 10-12 is shown a diagram of the heart rate control system and the equations which describe its behavior. It is known that a chemical substance norepinephrine, is released from sympathetic nerve endings when these



$$\frac{dA_1}{dt} = \frac{K_1 n f_1 + k_2(A_0 - A_1) + K_3(A_2 - A_1)}{V_1} \qquad \text{Eq. (i)}$$

$$\frac{dA_2}{dt} = \frac{K_3(A_1 - A_2) - dAB/dt}{V_2} \qquad \text{Eq. (ii)}$$

$$B + AB = \text{constant} \qquad \text{Eq. (iii)}$$

$$\frac{dAB}{dt} = K_4(A_2)(B) - K_5 AB \qquad \text{Eq. (iv)}$$

$$HR = HR_0 + K_6 AB \qquad \text{Eq. (v)}$$

FIG. 10-12. Diagram of a theoretical heart rate control system.

nerves are stimulated. The lag in the response to stimulation is accounted for by the assumption that the release of norepinephrine must diffuse to some active site in or on the cells of the S.A node. Here a second-order chemical reaction is assumed to take place between the norepinephrine and some substance, B, in order to account for the observed nonlinearities of the system. Equation (i) states that the rate of change of norepinephrine concentration (A_1) in the fluid surrounding the sympathetic nerve endings is equal to a constant (k_1) times the number of fibers (n) responding to each stimulus times the frequency of stimulation (f_1) plus a term which describes the equilibrium between the blood concentration A_0 and A_1 plus a term representing the diffusion of norepinephrine to the active site on the S.A. node (the pacemaker of the heart). Concentration of norepinephrine at this site is labeled A_2. Equation (ii) describes the rate of change of concentration A_2 as equal to k_3 times the difference between A_1 and A_2 minus the rate at which A_2 is combining with B to form compound AB. Equation (iii) states that B is a substance present in constant amounts whether it be

free or combined with A. According to Eq. (iv), the production of compound AB is a second-order reaction proportional to the product of A_2 and B. The reaction rate constants in each direction are k_3 and k_4. Finally, Eq. (v) expresses heart rate as equal to the initial heart rate plus k_6AB.

It might be just as logical to assume that the second-order chemical reaction between A and B occurs elsewhere in this system, for instance, at the nerve endings prior to the release of norepinephrine. This would introduce the same kind of nonlinearity into the response of the system. However, an experiment was performed which ruled out this possibility. The concentration of norepinephrine in blood (A_0) was raised to produce an increase in heart rate. Then f_1 was increased until the maximum heart rate was achieved. It was observed that the maximum heart rate achieved from sympathetic nerve stimulation was independent of the level of blood norepinephrine concentration. Unless the elevated blood norepinephrine concentration affected the amount of norepinephrine released by sympathetic nerve stimulation, this observation supports the concept that the factor which limited the maximum heart rate obtainable was not the amount of norepinephrine that could be released from the nerve endings but lay somewhere beyond this point as indicated by the mathematical model.

The constants for these equations may be uniquely determined by analysis of the response of two-step inputs in f_1 of different magnitudes. Once these parameters of the model have been so determined, this mathematical expression will predict the time course of heart rate resulting from any pattern of input f_1. Such prediction for four square-wave variations in input is shown in Fig. 10-13. This recording shows a comparison of the

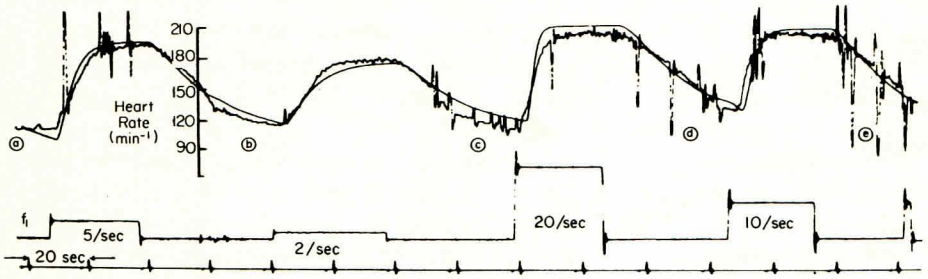


FIG. 10-13. Comparison of computer-predicted and observed variations of heart rate. Smooth curve represents computer predictions.

observed time course of heart rate generated in one section of an analog computer by measuring the reciprocal of time intervals between successive r waves of the electrocardiogram of a dog and the predicted time course of heart rate calculated in another part of the analog computer which had

been programmed to represent the mathematical model just described. The forcing function for the model equation was the analog signal labeled f_1. This is proprtional to the frequency with which the postganglionic sympathetic nerves to the dog's heart were being stimulated.

This model will also predict the time course of heart rate produced by sinusoidal and triangular variations in f_1. Although these equations predicted the time course of heart rate from a variety of input patterns, it cannot be concluded from kinetic information alone that the intermediary steps proposed in this hypothesis are necessarily those existing in the animal. Some other scheme might exist which has the same general form as these equations and, thus, would just as well describe the observations. This model does, however, predict certain phenomenon which can be checked with available techniques. A good example is the one referred to above; namely, the prediction that raising the concentration of norepinephrine in the circulating blood would not affect the maximum heart rate achievable by sympathetic stimulation.

Success in arriving at the appropriate form of the model and in deciding on the optimal set of parameters is dependent upon the investigator being able to obtain rapid solutions of the model equations which can be compared with experimental observation. To accomplish this, an analog voltage proportional to the input (f_1) and the output (HR) is recorded on a continuous loop of magnetic tape using frequency modulation. This tape is then reproduced at a faster speed than it was recorded; f_1 is used as a forcing function for the model in the analog computer and a dual-beam oscilloscope provides a means for continuous comparison of the predicted and recorded heart rate. The parameters of the model in the analog computer can then be adjusted empirically for optimal prediction. Table I

TABLE I

REPRESENTATIVE VALUES FOR EQUATION PARAMETERS OF THE ANALOG COMPUTER MODEL

$(k_1 n)(k_4) = 0.356$
$k_2 = 6.05$/sec
$k_3 = 0.25$/sec
$k_5 = 0.13$/sec
$k_7 = 2.75$/sec
$k_8 = 0.69$/action potential
$k_9 = 0.87$/sec

contains representative values for the equation parameters of this model. Using a similar approach, a model relating frequency of action potentials on the vagus nerve to the heart rate has also been devised.

B. Model of Baroreceptor Performance (Ridges *et al.*, 1964)

In the aortic arch and at the bifurcation of the carotid arteries are receptors which sense the stretch and the rate of stretch of these arterial walls. The input to these organs is the pressure in the artery and the output is the frequency of firing of the nerve fibers leaving the organs. The general form of the model of this system is shown by Eq. (2) below while Eq. (3) is an expanded form which takes into account the system nonlinearities.

$$F = A\frac{dP}{dt} + B(P - P_0) \tag{2}$$

will describe the frequency of firing (F) at a particular mean pressure level treating A, B, and P_0 as constants; F, of course, is limited to positive values.

$$F = a\left[(G - \bar{P})\overset{+}{\frac{dP}{dt}} + (\bar{P} - H)\overset{-}{\frac{dP}{dt}}\right] + b\left[\frac{P - (cP + P_0)}{K + P - (cP + P_0)}\right] \tag{3}$$

will describe the time course of frequency as a function of pressure (P) in the artery over a wide range of mean pressure levels. The positive and negative derivative terms are shown with a plus and minus sign over them since they are dependent in different ways on the mean pressure level in the system. Notice that the positive derivative term becomes less important as mean pressure in the artery rises while the negative derivative term influences frequency more when mean pressure is high. The hyperbolic form of the proportional term is thought to reflect the nonlinear pressure-volume relationship in the artery, a, G, H, b, c, K, and P_0 are constants which can be derived from an iterative solution of the model and comparison against the recorded frequency of firing. The mean pressure ($\bar{P}$) is defined by

$$\bar{p} + \tau\frac{dP}{dt} = P \tag{4}$$

where τ is a time constant of about 7 seconds and represents the time for the organ to adapt to a new mean pressure level in the system.

Figure 10-14 shows a comparison of the predicted and recorded frequency of action potentials from the carotid sinus nerve. The tracing at the bottom of the figure is the recording of the action potentials from the nerve fiber. Above this is the arterial pressure tracing and mean pressure is shown at the top. The two almost superimposed curves labeled frequency of action potentials are the theoretical and measured frequencies. Notice

the frequency of firing reaches a peak before the pressure reaches its maximum. The negative derivative term is evident by the pronounced dip during the rapid falling phase of pressure late in systole. This model is capable of describing the relationship between pressure and frequency of action potentials over a wide range of physiologic states in a given animal once the parameters have been determined at two mean pressure levels. However, there is a wide variation in these parameters from one dog to the next and studies are now under way to explore the physiologic correlates of these parameters.

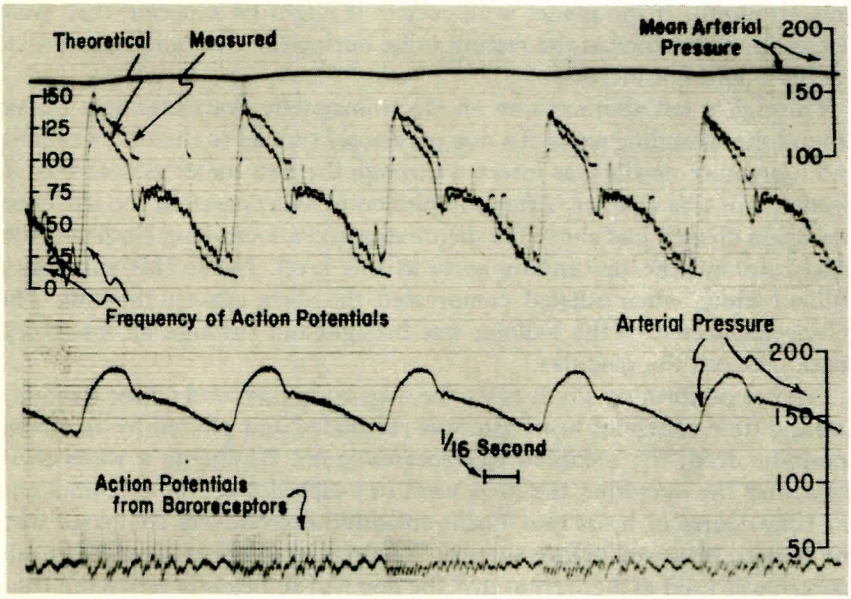


FIG. 10-14. Comparison of predicted and osberved frequencies of discharge of carotid sinus nerve.

A digital computer program has been written which solves the model equation using the averaged pressure wave form and averaged time course of frequency of firing obtained by a method described earlier in this chapter and illustrated in Fig. 10-5. This provides objective criteria for converging on the optimal set of parameters and eliminates the need for operator intervention and possibly bias in the process of finding these equation parameters. Of particular interest in this next phase of the study will be the determination of the physiological correlates for each parameter of the model, both in normal and disease states.

V. COMPUTER CONTROL OF A PHYSIOLOGIC VARIABLE IN AN ANIMAL

A. Analog Computer Control of Resistance to Blood Flow

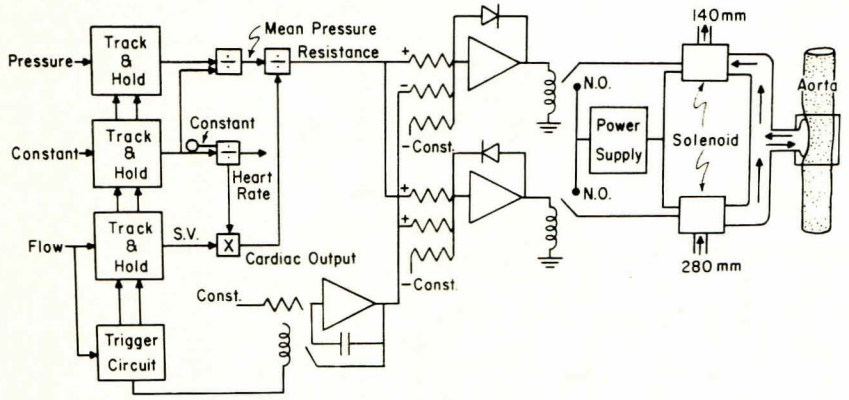
In the theory of cardiac output control described in Section II of this chapter and illustrated in Fig. 10-9, it is proposed that the prime cause for the increase in cardiac output during exercise is the fall in resistance to blood flow which occurs. To test this hypothesis an experiment was designed to permit control of total peripheral resistance in a dog running on a treadmill. If the model were correct it might be expected that, were resistance maintained at the resting value during the treadmill run, cardiac output would not increase.

Through a left thoracotomy an electromagnetic flowmeter was placed around the ascending aorta of a dog previously trained to run on a treadmill and a pressure needle was inserted through the flow meter as described in Section I of this chapter. After completion of this operation the left chest was again opened just above the diaphragm and a 5-cm-long cloth cuff was placed around the descending aorta at this level. Inside this cuff was a balloon which when inflated compressed the aorta against the cuff. The tubing connected to the balloon was brought out through an intercostal space between the scapulae.

Prior to performing any surgery the dogs were exercised on the treadmill and the time course of heart rate was calculated and plotted by an analog computer from the recorded electrocardiogram. Beginning a week or 10 days after the operation the dogs were run each day on the treadmill and the time course of heart rate during treadmill exercise was compared with the pattern observed before surgery. The return of the original heart rate pattern was used as a criterion that the dog had sufficiently recovered from the surgery to justify his being used for the experiments. A strain gauge pressure transducer was then strapped to the dog and connected to the polyethylene tube. Electrical signals from the strain gauge and from the electromagnetic flowmeter were fed to the analog computer and beat by beat calculations of stroke volume, heart rate, cardiac output, mean arterial pressure, and peripheral resistance over each heart cycle were made.

Figure 10-15 is a block diagram of the analog computer arrangement used to make these calculations and to control air flow into and out of the balloon. The resistance calculated with each heart beat is compared to a reference voltage in the computer. The two comparators are amplifiers with only a diode in their feedback paths. Each comparator is supplied with three signals: (1) the voltage representing peripheral resistance as calculated with each heart cycle; (2) a constant reference voltage; and (3) the output

voltage from an integrator whose input is a constant. This integrator which is triggered to zero with each heart cycle generates a saw tooth voltage which is fed to one comparator as a positive signal and to the other comparator as a negative signal. If the calculated resistance is greater than the constant, the output of the top integrator is a full 50 volts until the saw tooth voltage representing its third input reaches a value equal to the difference between the calculated resistance and the constant. At this point the output of the comparator falls to zero; thus, the gain of the integrator



SERVO CONTROL CIRCUIT

FIG. 10-15. Diagram of analog computer arrangement for servo control of resistance to blood flow.

determines the duration of each pulse for a given error signal. This 50-volt pulse operates a relay which closes the solenoid valve connecting the balloon to the low-pressure source for a time proportional to the difference between the resistance and the constant. If the resistance falls below the constant, a 50-volt negative pulse appears on the bottom comparator which allows air to enter the balloon. The track and hold circuits are set to trigger just after the end of systole as described in Section I (Fig. 10-2).

The concept of resistance as the ratio of pressure to flow is a meaningful index to outflow impedance from the central arterial bed only when steady-state or mean values for flow and pressure are used in the calculation; otherwise the capacitance and inertia of the system must be taken into consideration. For this reason values for flow and pressure must be averaged over a complete heart cycle before using them to calculate resistance. In a system such as this where the input to the controller is digitized to occur only at the end of each systole and the effect of the change induced in the

system by the controller cannot be measured until the next systole, it is important for stable operation that the change in resistance induced by the controller (computer plus balloon system) be completed as quickly as possible. In this system the computer control operation is complete in less than 0.1 second, which is considerably faster than the reflex adjustment taking place in the animal. It was found empirically that the most stable performance occurred when the low-pressure source was maintained at 140 mm Hg and the high-pressure source at 280 mm Hg.

In Fig. 10-16 is shown the response of a dog to treadmill exercise at 4 miles per hour on a 10% grade. In the first run done without computer control of resistance, heart rate rose 120% above the average resting value within 5 seconds while cardiac output at this time exceeded its resting

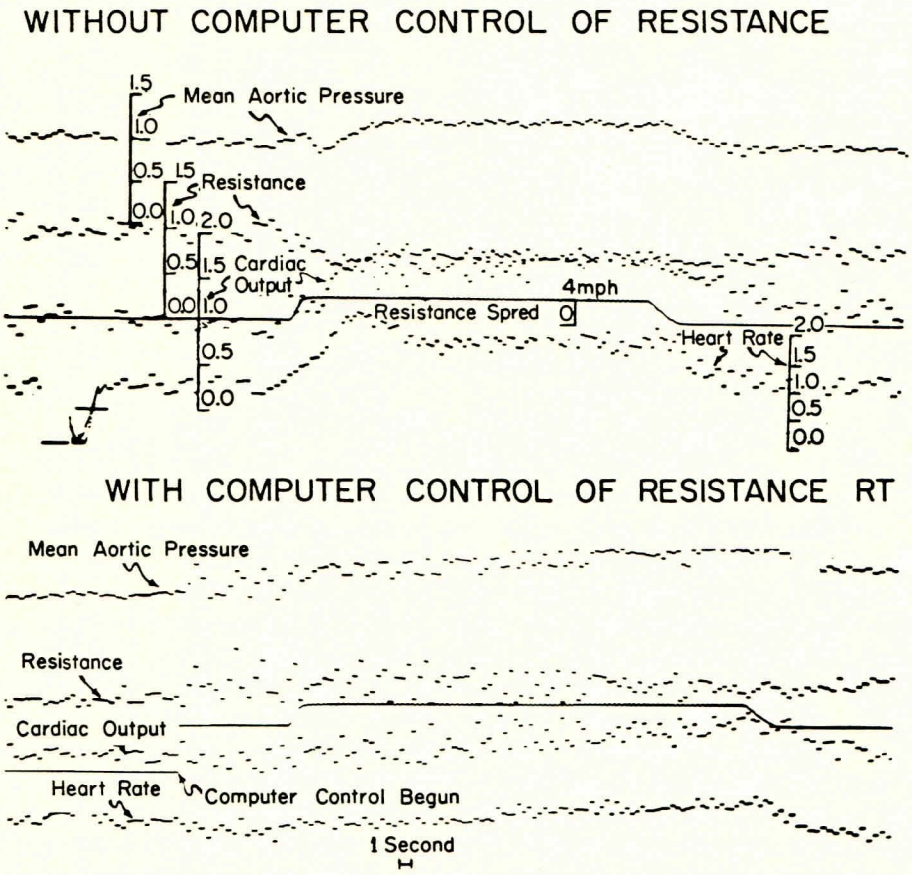


FIG. 10-16. Circulatory responses of a dog to treadmill exercise, without servo control (upper digram) and with servo control (lower diagram).

value by 70%. Calculated resistance fell to 60% of its resting value while arterial pressure fell 13% below and then rose 14% above the control after 8 seconds.

Three minutes after the completion of this exercise run the treadmill was started again at 4 miles per hour as shown in the bottom half of this figure. Just prior to starting the treadmill, however, the artificial resistance controller described above was activated by introducing a reference voltage slightly higher than the resting resistance to the comparator in the computer. This produced a small increase in measured resistance in the dog and increased the variation in resistance from beat to beat. The increased variation in resistance with computer control is due to the fact that the effect of the correction cannot be measured by the system until the end of the next systole. This introduces some instability into this artificial servo-loop. When the dog exercised under these conditions the fall in resistance was prevented by the action of the artificial controller. Heart rate rose only 10% above the resting value and cardiac output 12%. The transient fall in mean arterial pressure is not seen, the pressure rising 10% within 3 seconds after the onset of exercise.

The effect of turning the resistance controller on and off during an exercise run is shown in Fig. 10-17. As the controller is turned off resistance

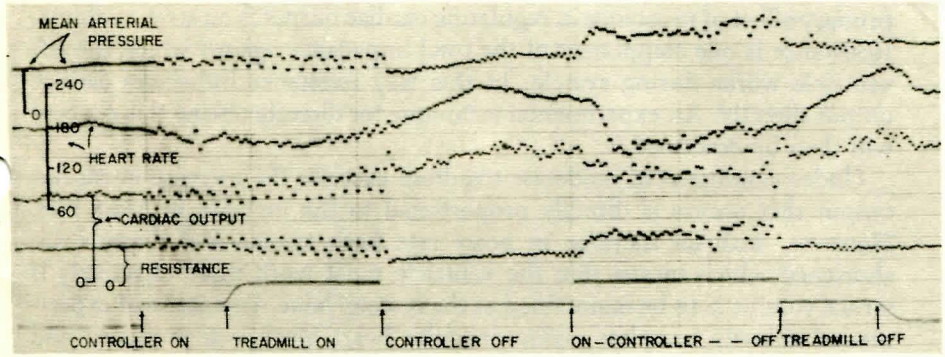


FIG. 10-17. Effect of turning servo control on and off during exercise.

falls immediately below the resting level and remains low while arterial pressure falls only transiently and then returns to its previous level. This return of pressure is due to an increase in heart rate and cardiac output. When the reference level for resistance in the computer is suddenly increased again (controller on), heart rate and cardiac output fall dramatically but not sufficiently to bring arterial pressure back to its original level. That this may be due to a change in the reference level of the dog's central

nervous system comparator (arousal) is supported by the fact that arterial pressure after turning the controller off 20 seconds later does not fall to the same level as during the previous controller off maneuver.

From this study it is apparent that a fall in peripheral resistance plays an important role in bringing about the increased heart rate and cardiac output that occurs in the early phase of exercise. Even though a drop in arterial pressure is not always observed with the onset of exercise, the fall in peripheral resistance does appear to a *sine qua non* for the production of a sustained increase in heart rate and cardiac output during exercise. There are, of course, inputs to the central nervous system other than the baroreceptors which are capable of increasing heart rate. In the context of the hypothesis here presented these inputs, such as excitement and anticipation of starting the treadmill, may alter the reference signal in the CNS comparator, but the fundamental determinant of cardiac output during moderate exercise is the state of dilatation or constriction of the blood vessels which in turn is largely dependent, during exercise, on the metabolic activity of the working muscles.

B. On-Line Simulation as a Means for Adaptive Control

Two experiments which will be described point toward the fact that the primary effect of resistance in regulating cardiac output is on stroke volume. Resistance is one component of the total impedance against which the left ventricle works during systole. In this way resistance influences cardiac output directly. An experimental technique for directly testing this concept will then be described.

Under conditions of moderate treadmill exercise the increase in cardiac output that occurs is directly proportional to the increase in heart rate. However, with an increase in heart rate both systole and diastole are shortened which means that the ventricle must work more effectively if stroke volume is to be maintained at the resting value. In a series of experimental animals complete atrioventricular heart block was produced and wires implanted into the right ventricle were attached to a stimulator which the dog carried on a harness. This was done to study systematically the effect of heart rate on stroke volume at a given treadmill speed. Heart rate was set at a given level 2 minutes prior to each treadmill run and cardiac output was determined by the indicator dilution method 2 minutes after the start of exercise. It was found at a given treadmill speed that cardiac output was independent of heart rate over a range of heart rates from 75 to 240 per minute. Thus, the animal was able to obtain a threefold variation in stroke volume in order to maintain his cardiac output. That the cardiac output was a function of the amount of exercise performed was shown by

the fact that cardiac output increased 40% when the treadmill speed was increased from 3 to 4 miles per hour (Warner and Toronto, 1960).

A second observation which suggests the domination of direct impedance over reflex effects in controlling cardiac output was made in a dog whose aortic arch had been stipped of its adventitia in order to destroy the afferent nerves from the aortic baroreceptors. Around the brachiocephalic artery, which gives rise to both carotid arteries, was placed a cloth-balloon constrictor for controlling pressure in the carotid arteries. Carotid artery pressure was sensed with a transducer and fed to the analog computer where it was averaged over each heart cycle. The average pressure was compared to a reference level (set point) and the difference resulting from this comparison controlled the balloon constrictor. Thus, by lowering the set point in the computer it was possible to lower the pressure in the carotid artery by any desired amount and maintain it at that level. The results of such an experiment are shown in Fig. 10-18. It can be seen that a lowering

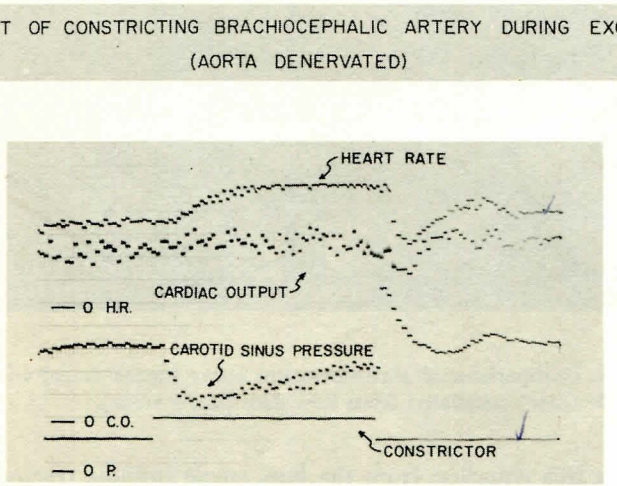


FIG. 10-18. Effect of lowering carotid sinus pressure by constricting the brachiocephalic artery on heart rate and cardiac output. The aorta has been denervated.

of carotid sinus pressure does bring about a reflex increase in heart rate but does not increase cardiac output. In fact, more commonly cardiac output decreases during such a maneuver, as would be expected if the total impedance that the heart sees during systole is the governing factor in controlling stroke volume.

To test this hypothesis adequately, it will be necessary to measure and control both the resistive and capacitive elements of the impedance which

the left ventricle sees during ejection. A simple model which relates pressure to flow is shown in Fig. 10-20 where P and F are the pressure and flow as functions of time in the ascending aorta, R and C are parameters representing lumped resistance and capacitance terms, and M is a constant related to the inertia of the blood column. That this expression is capable of describing the relationship of pressure to flow at a given physiologic state is shown by comparing in Fig. 10-19 the time course of pressure

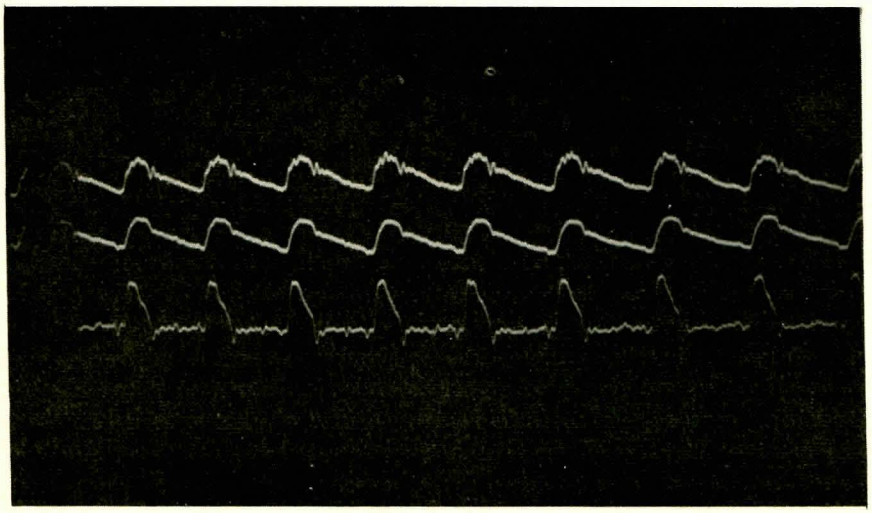


FIG. 10-19. Comparison of aortic pressure curve (upper trace) with predicted curves (middle trace) calculated from flow data (lower trace).

predicted by this equation from the flow curve (middle tracing) with the actual time course of pressure (top tracing). This simple model, however, does not take into account the fact that R and C vary with the physiologic state of the animal. A scheme has been devised which permits determination of optimal values for R and C by an iterative process well within the time required for one heart cycle. A block diagram of this is shown in Fig. 10-20.

The analog-to-digital (A-to-D) convertor samples both the pressure and flow transducer at 100 samples per second. When one complete heart cycle has been fed into the digital computer, the array representing flow as a function of time over that heart cycle is fed to the digital-to-analog (D-to-A) convertor at a rate of 10,000 samples per second. The voltage is fed to the

analog computer and serves as a forcing function for the model. The model solution, which is a prediction of the time course of pressure, is sampled simultaneously by the A-to-D convertor at 10,000 samples per second. In the digital computer a comparison is then made between the predicted pressure wave and the measured pressure wave over that heart cycle. Based on this comparison a new set of values for the parameters R, L, and C are derived and fed out through different channels of the

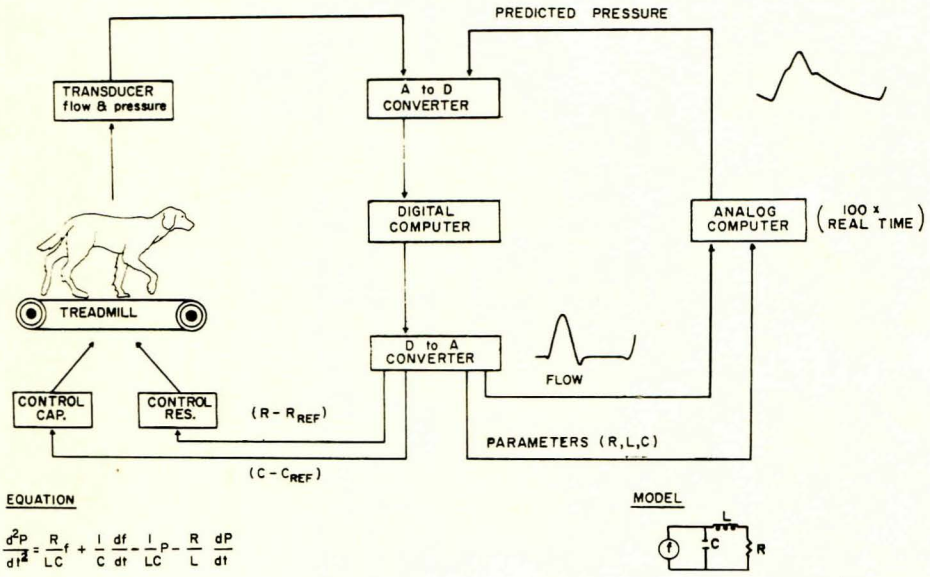


FIG. 10-20. Scheme for determining optimal R and C values in exercising animal.

D-to-A convertor to the analog computer where they serve as multipliers for the appropriate terms in the model equation. In the next solution this process is repeated until a solution is found which compares within prescribed limits with the measured pressure curve. At this point the parameters R and C are considered to represent the values of resistance and capacitance in the dog's aorta. These values are then compared to the appropriate reference values (average values with the animal at rest) and the differences are outputted through two other channels of the D-to-A convertor to the appropriate control devices in the animal. The resistance controller has been described. The capacitance controller presently being tested is a cylindrical balloon mounted around a catheter and inserted into the descending aorta. Air introduced into this catheter is compressed by

the aortic pressure and represents a capacitance element in parallel with the distensible walls of the aorta itself.

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